Lady Hayman

From: Mike McGovern

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POH(6)5512/87: Barbara Roache MP on Recombinant Factor VIII.

You asked for a background note about the management of people with haemophilia A, treatment with recombinant factor VIII and hepatitis C. This followed sight of a draft reply from you to Barbara Roache who wrote to you enclosing a letter from a constituent of hers about her 22 year old son with Haemophilia A and hepatitis C. The constituent is angry that her son cannot have treatment with recombinant factor VIII 'for cost effectiveness' reasons. Her letter outlines current numbers of people with haemophilia A who are not getting factor VIII, encloses literature on relative costs of the various factor VIII products available, makes comparisons between classical CJD transmission through pituitary derived Human Growth Hormone treatment and current treatment with plasma derived factor VIII, points to the inequity of current policy restricting provision of recombinant factor VIII to those under 16 years of age and new patients and requests that recombinant factor VIII be made available for all.

General background

Numbers of people with haemophilia
There are approximately 5400 people with haemophilia A in the UK. About half of these have severe disease which results in regular episodes of spontaneous bleeding into joints and muscles and following minor injury. These patients require regular treatment with factor VIII which is missing from their blood. Those with moderate or mild disease need significantly less treatment.

Development of treatments
With the advances in technology and treatment, management of people with severe haemophilia now includes regular or prophylactic treatment to avoid bleeding episodes and the long term consequences such as crippling arthritis. This is especially the case for younger people who commonly receive treatment three times a week rather than ad hoc treatment in response to specific bleeding episodes. In addition much of this treatment is given at home by the patients themselves or their families. As a consequence the requirement for factor VIII by haemophiliacs has risen especially since the early 1980s.

Purified plasma derived factor VIII products
Since the early 70s people with haemophilia have been treated with purified plasma derived factor VIII products which took over from various less specific plasma fractions in earlier use. In the UK these products were produced by the Bio Products Laboratory run by the National Blood Transfusion Service in England and by the Protein Fractionation Centre run by the Scottish National Blood Transfusion Service. These products were highly processed and licensed like all other pharmaceuticals by UK Health

Secretaries on advice from the Committee on the Safety of Medicines. In addition however because the UK was not self sufficient in the production of factor VIII a number of non UK sourced factor VIII products, largely produced by American Pharmaceutical companies were increasingly available.

Transmission of infections through blood products
Like blood these plasma products were associated first with the transmission of hepatitis B and non A non B hepatitis (NANB) later to become known as hepatitis C. A screening test for hepatitis B became available in the mid 1970s and largely eliminated transmission. NANB or hepatitis C remained a problem and in the early 1980s AIDS was recognised as transmissible through blood and blood products. A large proportion of people with haemophilia developed HIV infection and AIDS before it became possible to screen for the infection and to treat the plasma to prevent transmission. As AIDS was more prevalent in the US at the time factor VIII from there was responsible for the greater number of haemophiliacs infected. However since 1985 virally inactivated factor VIII has eliminated transmission of HIV and indeed Hepatitis C through plasma derived factor VIII.

From this history it is clear that the safety of products like factor VIII derived from blood cannot be guaranteed. While improving technology and screening have made these products very safe the risk of as yet unknown blood borne infectious agents which may not be inactivated by current processes being transmitted remains a possibility. This is of course the basis for the concern about new variant CJD.

The development of recombinant factor VIII
The development of recombinant factor VIII (and indeed recombinant factor IX) in the late 1980/ early 1990s and subsequent licensing of the product in the UK has heralded a new era in the treatment of haemophilia. For the first time the products are genetically engineered and the risk of infection is all but eliminated. This is verified in long term safety studies.

Supply and cost
However there are still problems of supply and cost. Recombinant factor VIII is produced by Baxter pharmaceuticals; as yet there is not enough to satisfy world wide demand and it is about twice as expensive in the UK as the now very safe plasma derived product. Several studies of its clinical and cost effectiveness have not persuaded many Health Authorities that it should be provided in preference to the plasma derived product. The extra cost to an average health authority of changing all patients with haemophilia A to recombinant treatment at current prices would be in the order of £5-700,000. This would bring the cost of treatment alone for the Health Authority to over £1,000,000. The extra cost to the Department would therefore be in the order of £50-70 million.

The Department's policy
The Department's policy has been that as the clinical and cost effectiveness of recombinant factor VIII has not yet been proven it is up to Health Authorities to decide on whether to fund it. And if they do so decide then this should be from the general allocations. However in February 1998, Secretary of State indicated that all children under the age of 16 and new patients with Haemophilia A should receive recombinant factor VIII. This decision was based on the fact that these patients would have been less

likely to have been exposed to infectious agents than older haemophiliacs and would consequently benefit most from recombinant product. The decision was influenced by the concern of the families of these children about the theoretical risk of nvCJD and as yet unknown infectious agents from plasma derived products and representations from the Haemophilia Society. It was agreed that funding for unplanned recombinant Factor VIII treatment in these patients in 1998/9 would be provided centrally but that from 1999 onwards this would come from central allocations.

Issues raised in the letter

Her son cannot have recombinant factor VIII 'for cost effectiveness' reasons.
It is strong Departmental and NHS policy that services and treatments be provided on the basis of cost effectiveness. This policy reflects the view of Sir Archie Cochrane that all effective treatments should be provided free to NHS patients. Plasma derived factor VIII products licensed in the UK have an extremely good safety record since viral inactivation was introduced in 1985 and are very effective. Nonetheless it is up to individual clinicians to decide on the best treatment for their patients and to persuade the Health Authority to support this. Many Health Authorities in fact already fund recombinant factor VIII.

While the cost differential between the plasma derived and recombinant products remains high in the UK the balance in favour of moving to recombinant factor VIII is unlikely to change quickly. This is despite the fact that compared with most other countries the price of recombinant factor VIII is lower here. Perhaps on account of the smaller profit margins to be gained by Baxter in the UK they are supplying more lucrative markets with their limited supply. The extra costs to other countries is also less in view of the relatively high cost of their plasma derived products.

Current supply of recombinant factor VIII to the UK does not meet demand and clinicians have difficulties in providing it within the new policy announced by Secretary of State. It is likely that this is another reason why Barbara Roaches' constituent's son at age 22 is not getting recombinant factor VIII as it is being reserved for younger patients who have most to benefit in that they will have had relatively limited exposure to blood borne infections. The fact that he is hepatitis C positive suggests that this is the case.

Literature presented on relative costs of the various factor VIII products
I do not know the source of this literature but it is misleading. Recombinant factor VIII while retailing at 52p per unit in fact is available to the NHS at 48p per unit. On the other hand the costs of various plasma derived factor VIII products range from 18 to 27p a unit and not 48p as suggested. This indicates that the differential is significant and cannot to be ignored.

Classical CJD transmission through pituitary derived Human Growth Hormone
The constituent is wrong when she suggests that this involved new variant CJD; it was in fact classical CJD. There is no evidence that nvCJD can be transmitted through blood and the risk remains theoretical. Acquiring nvCJD is related in time to the BSE epidemic and the science suggests that the agent that causes nvCJD in humans is identical to that which causes BSE in cattle. There are no cases of classical CJD reported in haemophiliacs despite prolonged treatment with blood products. However

The inequity of current policy
Restricting provision of recombinant factor VIII to those under 16 years of age and new patients is in fact an extension to the use of recombinant factor VIII. Secretary of State took this personal decision last February and this is outlined in the letter to the Haemophilia Society which Barbara Roache enclosed with her corespondents letter. Up then the policy was purely evidence based -that recombinant factor VIII showed no effectiveness benefit over plasma derived and that if Health Authorities wished to support prescription they would have to do so out of existing resources. Many in fact have done this. Secretary of States' statement and the following Health Services Circulars made it clear that the decision was made on humanitarian rather that effectiveness grounds. That is not available to all, does raise questions of equity but these can be justified on the basis that those who will gain most from recombinant factor VIII treatment are those who have had least exposure to plasma derived product especially those who were not treated before effective viral inactivation was introduced in 1985.....in other words new patients and those under 16 years of age.

Recombinant factor VIII should be made available for all people with haemophilia A.
There are three issues -clinical effectiveness, availability and cost. Clinical effectiveness: quite simply, no study to date has demonstrated that recombinant factor VIII is good value and this is the Department's current position. This is likely to change when/if prices fall. Availability: the product is made by Baxter laboratories and demand currently outstrips supply. There is not enough of the currently licensed recombinant factor VIII to support treatment of those under 16 and new patients. Other second and third generation products are under development and it is likely that the companies are depending on unsatisfied demand for the Baxter product to drive sales of these ever newer and more expensive products. Cost: the likely extra cost of providing recombinant factor VIII to all people in England with haemophilia A would be in the order of £50 million pa, bringing the average total cost of treatment alone for these 2,000 patients to £77-80 million pa.

Local negotiation on treatment
Barbara Roaches constituent's sons age is 22 and he is hepatitis C positive. From the framing of the letter it would appear to me that the family have already discussed the issue with the treating clinician. The words used 'cost effectiveness' quite clearly indicate that they have been advised that recombinant factor VIII in this case is not an option on the basis of clinical benefit. Clearly the mother thinks differently. However just because the Secretary of State or the Department do not support a policy that recombinant factor VIII be provided for all patients does not mean that clinicians cannot prescribe it or Health authorities should not pay for it. As indicated already many health Authorities do just this. This was the basis for the advice to the family to discuss the situation with the local haemophilia director again. However the main issue remains that the evidence that recombinant factor VIII is more effective than plasma derived has not been forthcoming Those providing care have to do so in the context of local need. Affordability unfortunately is part of this consideration especially in areas of high cost treatments. This is the kimnd of area which NICE will address when this is set up later this year.

Dr Mike McGovern